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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/399,120	09/20/1999	DESMOND MASCARENHAS	220952029300	1886

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EXAMINER	
GUPTA, ANISH	
ART UNIT	PAPER NUMBER
1653	15

DATE MAILED: 05/21/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/399,120	MASCARENHAS, DESMOND	
	Examiner	Art Unit	
	Anish Gupta	1653	

-- The MAILING DATE of this communication appears on the cov r sheet with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 February 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *11-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The amendment filed, 3-12-02, is hereby acknowledged. The amendment amended claim 1. Claims 1-16 are pending in the application.

2. Applicant's election without traverse of Group I, claims 1-10 and 16 in Paper No. 8 is acknowledged. Claims 11-15 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Group II, there being no allowable generic or linking claim. Election was made without traverse in Paper No. 8.

3. The arguments filed 3-13-02, to the outstanding rejection, have been considered. The rejections have been rewritten to provide further elaboration for the reasons for rejections. The arguments made have been addressed to the extent they are applicable to the current rejection. Further, any rejection cited in the previous office action and not cited herein is hereby withdrawn.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112
First Paragraph

5. Claims 1-10 and 16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention:

The invention is drawn the use of "null IGF-1" peptides in the treatment of cancerous tumors by inhibiting their growth

(2) The state of the prior art

The art indicates that native IGF-1 induces rather than inhibits tumor growth. The art has recognized that modified IGF-1 analogs, analogs that have replaced amino acids in positions 24, 31, or 60, have a loss of affinity for the 1 IGF receptor but retain affinity for type 2 IGF receptor. The art, however, does not recognize that replacement of amino acids in IGF-1 receptor will result in an activity that inhibits the growth of cancerous tumors.

(3) The relative skill of those in the art

The relative skill of the those in the art is high.

(4) The predictability or unpredictability of the art

Applicants activity is based on the structure of the peptide. Since the activity is based on structure the predictability in the art is low. This due to the fact the art has recognized the difficulty in determining the three dimensional structure of a peptide solely based on structure. Ngo et al. teach that for proteins and peptides, a " 'Direct' approach t structure prediction, that of directly simulating the folding process, is not yet possible because contemporary hardware falls eight to nine orders of magnitude short of the task." (see page 493 in Ngo et al.) Accordingly, it is not known if an efficient algorithm for predicting the structure exist for a protein or peptide from it amino acid alone (see page 492 in Ngo et al.). Similarly, the Rudinger article (see the conclusions in particular) states "The significance of particular amino acids or sequences for different aspects of biological activity cannot be predicted a priori but must be determined from the case to case by painstaking experimental study."

(5) The breadth of the claims

The claims are drawn to a method of using "uncomplexed null insulin-like growth factor." The specification defines null IGF-1 as IGF-1 which has amino acid sequence alteration at one or more sites in the molecule (see page 5 of the specification). Further, Null-IGF-1 retains its activity in its ability to bind IGFBP-3, but is altered in its receptor binding and/or activating properties. The sequence of native IGF-1 contains 70 amino acids. Thus, the claims are drawn to the use of any IGF-1 analog wherein one of the amino acids have been altered in the in the native sequence.

(6) The amount of direction or guidance presented and (7) The presence or absence of working examples

Although the specification provides guidance on how to make the peptides of the claimed invention, the specification has not provided ample guidance the effectiveness of peptides as inhibiting the growth rate of a tumor. As stated above, the specification implies that any sequence wherein the IGF-1 peptide has a differing amino acid from the native sequence will be effective in inhibiting the growth rate of a tumor. The working examples are limited to a single peptide, Y60L IGF-1, which was shown to be affective against prostate cancer. The specification does not disclose other modified peptide that are effective against tumor growth or disclose the effectiveness of peptide against different tumors. Although working examples are not necessary, it has been held that in unpredictable art, such as chemical cases more may be required. In re Dreshfield, 110 F.2d 235, 45 USPQ 36 (CCPA 1940), gives this general rule: "It is well settled that in cases involving chemicals and chemical compounds, which differ radically in their properties it must appear in an applicant's specification either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that the chemicals or chemical combinations included in the claims are capable of accomplishing the desired result."

The specification has not provided any amino acids position, in the native IGF-1, that need to be maintained or should be avoided in-order to obtained the desired activity. The activity is solely based on structures that have altered receptor binding activity. One cannot predict if a given modification in a peptide will have desired results in the inhibition of tumor growth. As stated previously, "'Direct' approach to structure prediction, that of directly simulating the folding process, is not yet possible because contemporary hardware falls eight to nine orders of magnitude short of the task. '(see page 492 in Ngo et al.) Accordingly, it is not know if an efficient algorithm

for predicting the structure exist for a protein or peptide from it amino acid alone (see page 492 in Ngo et al.). Although the reference does not entirely rule out the algorithm, Ngo states that too many variables exist in obtaining an efficient algorithm. For example, the "Not knowing the computational complexity of side chain structure predication leaves the algorithm developer in the quandary of not known whether inexact methods are truly necessary..." (see page 495). Therefore, clearly one could not predict the three dimensional structure based on structure of peptide alone. Moreover, the true fact of the state of the art in peptide chemistry is expressed succinctly in the Rudinger article (see the conclusions in particular). "The significance of particular amino acids or sequences for different aspects of biological activity cannot be predicted a priori but must be determined from the case to case by painstaking experimental study." It should be noted that reference of Bayne et al. (J. Of Biol. Chemistry, Vo. 265, No. 26) teach that replacement of Tyr 24 and/or Tyr 31 in IGF-1 affected the binding activity of the peptide to the IGF-1 receptor. However, the reference further states that it could not be concluded "from our data whether the changes in affinity upon replacement of residues Tyr24 and/or Tyr31 are due to side chain or main chain interactions with the type 1 IGF receptor." (See page 15651). This implies, again, that one of ordinary skill cannot predict if the activity based on structure alone. As stated above, the specification has not provided any guidance as to what amino acids additions and/or amino acid changes should be avoided and/or desired. The only guidance provided in the specification is that the activity, with respect to the Type 1 receptor is, is altered such that there is "little or no binding" to the receptor. The specification does not set forth assay models whereby one could reasonably determine if the modification achieved the desired "little or no binding" to the type 1 IGF-1 receptor. It should be noted specification does not provide any guidance as what would constitute

little binding affinity for the IGF-1 receptor. Thus one would be burdened with undue experimentation to determine which peptides, out of numerous possibilities, would be effective in achieving tumor growth suppression.

Finally, as stated in the previous office action, the claims are drawn to the treatment of all cancers. However, the specification has only shown effectiveness towards on single type of cancer. It is well known that the all cancers to not have the same mechanism of development and growth. Thus one could not assume that an agent effective against one tumor would be effective against all types of tumors. In their response, Applicants stated that claim 1 was amended to "more clearly define the present invention." However, the amendment has not addressed the issue of the effectiveness of Null IGF-1 against all types of tumors.

(8) The quantity of experimentation necessary

Since, the is uncertain to predict the helical structure of amino acid sequences based on structure alone, since contemporary hardware falls eight to nine orders of magnitude short of the task, and since different aspects of biological activity cannot be predicted a priori but must be determined from the case to case by painstaking experimental study, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to determine if the peptides would be effective in slowing the growth rate of tumors in a subject having cancer.

Claim Rejections - 35 USC § 112
Second Paragraph

6. Claims 7-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims recite that a specific position is replaced in the "null IGF-1." However, the based claim does not recite any specific sequence depicting various positions. Thus, there is insufficient antecedent basis for the limitation concerning positions in the base claim.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anish Gupta whose telephone number is (703) 308-4001. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can normally be reached on (703)308-2923. The fax phone number of this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Christopher S. Low

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5/14/a

Anish Gupta